B3 throughout the total analgesic drug [electrotransport] iontophoretic delivery period wherein the analgesic drug is delivered through the body surface.

REMARKS

In the Official Action, the Examiner withdrew the finality of the previous Action, and rejected the claims over certain prior art combinations. With respect to the first ground based on Weaver et al, U.S. Patent No. 5,019,034, or Sibalis et al, U.S. Patent No. 4,878,892, in view of Levy et al, U.S. Patent No. 4,822,802, the Examiner essentially took the position that the unexpected results provided in the evidence of record were based on iontophoresis and could not be applied to electroporation/electrosmosis which were encompassed by the term "electrotransport". In addition, the Examiner maintained the rejection based on Phipps et al, U.S. Patent No. 5,423,739, and Phipps et al, U.S. Patent No. 5,125,894, and the reference contained in the latter patent to the Padmanabhan et al article.

By the present Amendment, the claims have been amended to specify that the invention relates to iontophoresis thereby rendering consistent the evidence and the scope of the claims and meeting the stated concern of the Examiner. In addition, the claims have been amended to clarify that the recited level of concentration is maintained throughout the total iontophoretic delivery period. This latter recitation is in response to the Examiner's first raised point concerning the use of multiple dosages in the art. While it is believed that the original language conveyed the proper understanding of the invention when considered in light of the specification, the amendment renders more clear

that the recited concentration is to be maintained throughout the total delivery period and not just a portion thereof.

The reliance on the cited documents and the comments in the Action, particularly referring to alleged safety and inoperativeness, indicate that a further discussion is in order. When one is designing an iontophoretic delivery device, the donor reservoir is selected depending on various factors including the amount of the drug to be administered. For a given amount of drug to be administered, if one doubles the liquid volume of the donor reservoir, the drug concentration will be halved. Therefore, there is a substantial difference between the amount of drug and the drug concentration in the donor reservoir.

On page 2 of Dr. Phipps' Declaration that was submitted with the previous response, he notes that it was well known that diffusion of fentanyl and sufentanil substances through the skin was possible without the application of current, especially if the system were inadvertently applied to a skin site with compromised barrier function and that it was also well known that the rate of diffusion of a substance across the skin could be decreased by decreasing the drug concentration. He accordingly concluded that low concentrations would be desired to minimize diffusion (i.e., passive delivery) when an electrotransport device is not transmitting current to the skin.

Dr. Phipps' explanation does not mean that known devices were inoperative. Quite to the contrary, because of the understood phenomenon of passive delivery, those skilled in the art would be led to design iontophoretic delivery devices for delivering potent drugs, such as fentanyl or sufentanil, with low concentrations in the donor

reservoir to reduce the rate of passive delivery. Dr. Phipps further explained that it was desired that the donor reservoir contain only the amount of drug needed for treatment of the patient to minimize the potential for inadvertent misuse or abuse of a "used" system. Both of these points were raised to provide an understanding of why the present invention goes against conventional wisdom in the art in order to achieve the advantageous results discussed in the specification and during the prosecution of the present invention.

More precisely, by following the teachings of the present invention, one can meet the problem of maintaining a predictable transdermal iontophoretic flux for fentanyl and sufentanil at a particular applied current level. This significant result is attained by going against conventional wisdom and maintaining the concentration of a fentanyl salt in an aqueous solution in the donor reservoir at a level above about 11 mM or by maintaining the concentration above about 1.7 mM when the drug is a sufentanil salt. At such levels, the iontophoretic flux can be maintained at an essentially constant level substantially throughout the total analgesic drug delivery period wherein the analgesic drug is delivered through the body surface. As pointed out in the previous response, it is important to understand that the defined relatively high concentration of fentanyl salt or sufentanil salt is maintained during the delivery period and that delivery is terminated before the contents of the reservoir are depleted. In other words, the device would be removed from the patient even though a substantial amount of drug remains in the donor reservoir.

With a proper understanding of the present invention, applicants believe that it is clear that the claims now of record cannot be rejected over the cited prior art. In particular, neither Weaver et al nor Sibalis et al in any way relate to the iontophoretic

delivery of fentanyl salt of sufentanil salt. In fact, Sibalis et al specifically distinguishes the delivery of other materials in the passage at column 1, lines 26-50 and distinguishes iontophoresis in column 7, lines 1-7 in describing the electrolytic transdermal delivery of polypeptides. Similarly, Weaver et al distinguishes over techniques, including iontophoresis, in columns 1 and 2 and instead relates to a process involving electroporation.

While such differences should be sufficient to distinguish the presently claimed invention, applicants maintain that it is improper to attempt to combine the teachings of these patents with Levy et al, which although describing the transdermal administration of fentanyl and sufentanil, relates to a passive transdermal system involving the administration of unionized drug which is known in the art to be significantly different from electrotransport systems. Indeed, since a passive system does not utilize transport current, there is no need to be concerned with obtaining a predictable transdermal iontophoretic flux for fentanyl and sufentanil at a particular applied current level. Thus, even if the patents could be combined, the combination would not lead one of ordinary skill in the art to the present invention or an appreciation of the advantages which can be attained therefrom.

The Examiner's reliance on the two Phipps et al patents is believed to be based on an inadvertent misunderstanding of certain portions thereof and the Padmanabhan et al article cited in the '894 patent. Neither of the Phipps et al patents specifically relates to the iontophoretic delivery of fentanyl or sufentanil and neither discloses the challenge which these highly potent drugs present. Indeed, the '894 patent does not even mention

these drugs and the '739 patent only mentions them in a long list of other active agents which extends over columns 13 and 14. Therefore, other than improper reliance on applicants' own specification, there is no reason why one of ordinary skill in the art would refer to only the claimed drugs from amongst the many that are described in the '739 patent.

In addition to the foregoing shortcomings, neither of the Phipps et al patents teaches the claimed concentration levels of fentanyl salt or sufentanil salt which are to be maintained substantially throughout the total delivery period wherein the analgesic is delivered through the body surface in order to avoid a substantial decrease in normalized flux. Keeping in mind the explanation by Dr. Phipps in his Declaration, it would actually be contrary to conventional thinking to terminate drug administration after the total delivery period while the concentration of fentanyl and sufentanil salts are substantially at the defined levels. Hence, the Phipps et al patents would not lead those of ordinary skill in the art to the presently claimed invention.

The '894 patent has been relied on to show the effect of concentration of drug ions on the rate of drug delivery at constant current as set forth at column 11, lines 8-16. This passage states:

> In general, although rate of drug delivery is proportional to current, at a constant current the rate of drug delivery (R_d) is independent of drug concentration (i.e. target species concentration) in the active electrode reservoir, provided that the concentration is at least above a threshold level (and little or no extraneous ions are present); see Padmanabhan, R. V. et al *J. Controlled Release*, supra.

This statement in the patent would actually lead away from the present invention since it teaches that electrotransport flux is independent of drug concentration as long as a

small amount of drug is present in the reservoir. This proper understanding is evident from the cited Padmanabhan et al article that has previously been made of record.[1] The article refers to tests using hydromorphone and in the passage beginning on page 129, the article describes tests to determine if hydromorphone concentration in the donor solution affected the rate of delivery. After testing a wide range of solution concentrations, the article observes that "No significant difference in steady-state rate was observed over this broad concentration range." This conclusion was supported by the determination that:

> Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

In other words, the article teaches that unless the donor reservoir is substantially totally depleted, i.e., the threshold level, the concentration in the reservoir does not have an effect on the rate of delivery. This explicit teaching would lead those skilled in the art that one could administer drugs by iontophoresis at a constant current until the donor reservoir was substantially depleted without variation of the drug flux.

Despite this teaching and other teachings in the art, such as in the Kasting et article which similarly concludes that "...the efficiency of drug delivery ...is independent of drug concentration in this example", applicants have found that one must maintain the concentration of fentanyl and sufentanil far above the depletion level in order for constant flux to be obtained for constant current. Indeed, in the case of fentanyl, which is many

---

[1] The inadvertent omission of the Kasting et al article is regretted and a copy of the article is provided herewith.

times more potent than hydromorphone, the concentration must be above about 11 millimolar.

The claimed levels are completely unexpected in view of the plain teachings in the art that for a given current, flux is independent of drug concentration in the donor reservoir unless the drug in the donor reservoir is totally depleted. Furthermore, given the potency of the claimed drugs, it would be contrary to conventional wisdom to deliberately design an iontophoretic system with a high concentration of the drugs and to deliberately terminate the total delivery period while there is a substantial amount of these potent drugs in the donor reservoir. Thus, without improper resort to applicants' own specification, the cited prior art would not lead to applicants' invention or an appreciation of the advantageous results which can be attained therefrom.

Accordingly, based on the claims and evidence of record, applicants respectfully submit that the present invention is patentable in all regards and therefore request entry of the instant Amendment and reconsideration and allowance of the present application.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Robert G. Mukai
Registration No. 28,531

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: October 24, 1997

RECEIVED
97 OCT 24 PM 4:11
GROUP 330